Anti-/Propsychotic Drug Signaling via Heteromeric GPCRs—A Balancing Act?

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In this issue, Fribourg et al. provide insight into a molecular basis of psychosis. They reveal that a heteromeric complex formed by the G protein-coupled receptors (GPCRs) for glutamate and serotonin is a convergent site for the activity of anti- or propsychotic drugs, opening a possibility for new therapeutic strategies for schizophrenia.

Psychosis is a brain condition that includes hallucinations, delusions, and disorganization of semantic content of speech and writing due, in part, to disturbances in perception and other higher brain functions. This is also described as loss of contact with reality. Psychosis occurs in many brain conditions with distinct etiologies, such as substance abuse and brain injury, and it is well-known as a key manifestation of schizophrenia, a devastating chronic mental illness that affects about 1% of the global population. In this issue of *Cell,* a study reveals that a heteromeric complex formed between the metabotropic glutamate 2 receptor (mGluR2) and the serotonin 5-HT_{2A} receptor (2AR) integrates the actions of drugs that exert positive and negative influences on psychosis (Fribourg et al., 2011). 2AR is a Gq-coupled GPCR that responds to serotonin, whereas mGluR2 is a Gi-coupled GPCR that responds to glutamate.

Following the serendipitous introduction of chlorpromazine for treatment of psychotic patients in the early 1950s, investigators studied the pharmacological mechanism of chlorpromazine and related compounds. They proposed that the blockade of dopamine D2 receptors (D2R) by these "classic or typical neuroleptics" predicts clinical and pharmacological potencies (Creese et al., 1976). More recently, clozapine and a group of compounds called "atypical or second-generation neuroleptics" have emerged. These compounds are generally more effective for treating psychosis than the classic neuroleptics. In addition, these atypical neuroleptics show high affinity for the 2AR over the D2R. Although many psychedelic drugs, including LSD, also target 2AR, some compounds with high affinity for 2AR do not influence psychotic manifestations, indicating that the precise role of 2AR in psychosis is yet to be elucidated. In the past decade, another class of drugs, the mGluR2/3 agonists, have gained attention for their amelioration of schizophrenia-like behaviors elicited by phencyclidine in rodents (Moghaddam and Adams, 1998). In some clinical trials, these same compounds have shown some therapeutic effects on patients with schizophrenia (Patil et al., 2007).

A previous report illustrated that the 2AR and mGluR2 receptors physically interact in pyramidal neurons of the somatosensory cortex (González-Maeso et al., 2008). In this issue of *Cell*, Fribourg et al. investigate the intracellular signaling properties of the mGluR2/2AR heterocomplex in *Xenopus oocytes* and show that the heteromeric assembly of 2AR and mGluR2 enhances Gi signaling and reduces Gq signaling. The authors introduce a metric called the balance index (BI), which describes the balance of Gi and Gq signaling, and demonstrate that ligand binding to both mGluR2 and 2AR alters the BI (Figure 1). Most importantly, the investigators observe that the BI can predict the anti- or propsychotic activities of drugs targeting mGluR2 and 2AR. Drugs with the most effective antipsychotic properties, regardless of which receptor they target, have high BI values, whereas drugs with the most effective propsychotic properties have low BI values. With a rodent model of psychotic-like behaviors elicited by MK801, a noncompetitive antagonist of the NMDA-type glutamate receptor, the authors demonstrate that both 2AR and mGluR2 are required for the antipsychotic action.

This intriguing work sets the foundation for future work and raises important questions. This study uses knockout mice to elegantly illustrate the interdependency of mGluR2 and 2AR for binding drugs. However, it is still unclear in which specific cells these two GPCRs form the heteromeric assembly within the brain. Cell type- and/or region-specific knockout mice may be useful to further address this question.

Building on the demonstration that clozapine (targeting 2AR) and LY37 (targeting mGluR2) promote antipsychotic-like behavior by targeting this heteromeric complex, an important follow-up question is whether other atypical neuroleptics (e.g., olanzapine and risperidone) and other drugs that target mGluR2 elicit the same effects on psychosis-relevant behavioral changes as predicted by the BI. This question is important when we consider the historic studies by Snyder, Seeman, and others that demonstrated the actions of nearly 30 different classic neuroleptics via D2R. They showed that the relative affinity of these D2R antagonists strongly correlated with therapeutic potency. Moreover, all of these drugs were specific for the D2R, while lacking correlation with histamine, serotonin, and other receptors (Creese et al., 1976). To further test the predictions of the BI, the application of a recently described assay for testing impaired detection of

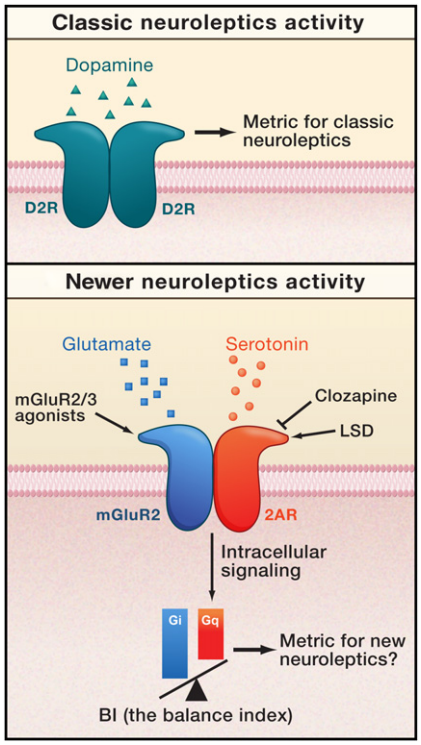

Figure 1. Comparison between Classic Neuroleptics and Newer Classes of Antipsychotics

Clinical potency of classic neuroleptics has been understood on the basis of affinity to the dopamine D2 receptor (D2R) (upper panel). In contrast, Fribourg et al. propose that the intracellular Gi and Gq signaling balance (BI), downstream of a heteromeric complex composed of the serotonin 5-HT_{2A} receptor (2AR) and metabotropic glutamate 2 receptor (mGluR2), provides a potential new metric for predicting the anti- or propsychotic activity of drugs targeting 2AR and mGluR2 (lower panel).

reality in rodents (McDannald et al., 2011) will provide another, perhaps more relevant, behavioral readout.

Fribourg and colleagues propose a combined medication regime of glutamate antipsychotics and atypical neuroleptics (e.g., clozapine) at suboptimal doses. Such treatments may result in sufficient efficacy due to a synergistic action via the mGluR2/2AR heterocomplex and could minimize the side effects that come from normal doses of these compounds, especially the metabolic problems elicited by atypical neuroleptics. To consider this idea in a clinical sense, we must pay careful attention to the fact that these two classes of compounds may also have independent pharmacological actions from those regulated by the mGluR2/2AR complex. Convergence of cellular cascades downstream of receptors for dopamine, glutamate, and serotonin was also explored in the study of phosphodiesterases (PDEs) in the context of molecular understanding and drug discovery for schizophrenia (Menniti et al., 2006).

Many conditions accompanying psychosis, especially schizophrenia, occur after puberty or in young adulthood, and therefore fundamental open questions concern the neurodevelopmental trajectory in these conditions. In particular, it will be interesting to explore a potential role for the mGluR2/2AR complex during neurodevelopment, utilizing animal models that manifest neurodevelopmental susceptibility with some relevance to psychiatric illness (Brandon and Sawa, 2011).

Recently, schizophrenia research has focused on cognitive deficits, which can predict long-term disability. Nonetheless, in real clinical settings, psychosis is still a major problem with a substantial fraction of patients showing resistance to all repertoires of neuroleptics currently available. Thus, the proposal of this new potential metric (the BI), which might be used in drug screening for psychosis, is timely and significant in offering a new way to think about treatments. Going forward, it should be important to validate the BI with a combination of pharmacology, genetics, molecular neurobiology, and brain imaging (e.g., Sawa and Snyder, 2002). Moreover, the findings of Fribourg and colleagues go beyond the scope of neuropsychopharmacology and clinical psychiatry, impinging on the biology of cell signaling and demonstrating the significance of GPCR heteromerization in cellular and behavioral responses.

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